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Minor bleeding in patients with atrial fibrillation using a non-vitamin K antagonist oral anticoagulant

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Author contributions
DM, EvR: initiated and designed the research; DM, RF: gathered data; NV: performed statistical analysis; DM, EvR: analysed results; DM, RF, NV, EvR: wrote the paper.

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None reported.

ABSTRACT

Aims

We sought to investigate the magnitude of minor bleeding and identify risk factors for minor bleeds during non-vitamin K antagonist oral anticoagulant (NOAC) therapy.

Methods

This was an observational cohort study of patients with atrial fibrillation (AF) referred to a regional NOAC outpatient clinic between February 2013 and October 2017. The study population consisted of 875 consecutive patients with AF who visited the NOAC outpatient unit to initiate treatment with apixaban (N=303), dabigatran (N=267) or rivaroxaban (N=305) for long-term ischemic stroke prophylaxis. Minor bleed was defined as every overt bleeding that does not fulfil the criteria of major or non-major clinically relevant bleeding according to the International Society on Thrombosis and Haemostasis.

Results

Overall rate of minor bleeds was 19.2 per 100 patient years of follow up. Bleeding rates for apixaban, dabigatran and rivaroxaban were 26, 8.3 and 23 per 100 patient-years of follow-up. Next to the type of NOAC, the main risk indicators for minor bleedings during NOAC therapy were a HAS-BLED score of 3 or higher and novel anticoagulant use (no history of vitamin K antagonist use).

Limitation

This was a retrospective observational study evaluating NOAC treatment in a non-randomized setting.

Conclusion

Our data showed that minor bleeds are common in novel NOAC users, especially when using apixaban and rivaroxaban. In the latter two NOACs, hematoma (bruises) and nose bleeds were more frequently observed and accounted for the difference with dabigatran. Besides type of NOAC, a higher HAS-BLED score and novel anticoagulant drug use were associated with an increased risk of minor bleeding.

KEYWORDS: NOAC; minor bleeding; anticoagulants, apixaban, dabigatran, rivaroxaban

INTRODUCTION

Non-vitamin K antagonist anticoagulation drugs (NOACs) entered the market in the US/EU beginning in 2009. Non-vitamin K oral anticoagulants such as apixaban, dabigatran, edoxaban, and rivaroxaban are direct selective inhibitors of activated coagulation factors X or II. NOACs have a good dose-response relationship that eliminates the need to closely monitor coagulation levels. Several studies have confirmed the superior or similar efficacy and safety of NOACs over vitamin K antagonists (VKA) with respect to stroke and systemic embolic events (SEE), myocardial infarction, all-cause mortality and major-,intracranial- or gastrointestinal bleeding[1,6,7,8,9].

Given the increasing number of patients using a NOAC, patients experience with this class of drugs in real life is very important [2]. In a previous study we investigated the reasons why patients discontinue NOAC therapy. Next to lack of tolerability (side effects), the occurrence of minor bleeding was a major reason for the NOAC discontinuation.

There is still not much known about minor bleeding in real life practice among atrial fibrillation patients. Firstly, NOACs are relatively novel and available knowledge mainly comes from large studies that focus on major bleeds, ischemic strokes and mortality. In this, evidence on the differences in patterns of minor bleeding between NOACs is scarce, as well as potential risk indicators for minor bleeding. From Dresden NOAC registry we only know that more than 60 % of all rivaroxaban associated bleeding complications were found to be minor bleeding events[3]. Incidence rate of minor bleeding was 35.8 (95% Confidence Interval 32.2-39.7) per 100 patient years, clinically relevant non-major bleeds 20.7 (CI 18.1-23.5) and for major bleeds 3.1 (CI 2.2-4.3) per 100 patient years. This 10 fold higher occurrence of minor bleeds has a major impact on patients quality of life. Given the lifelong indication of NOAC in atrial fibrillation almost every patient has a great chance of experiencing minor bleeds during his or her treatment.

The central aim of this study was to investigate the "occurrence pattern" of minor bleeds (rates and types), as well as the presence of risk indicators for minor bleeding.

METHODS

Study population

In this study, all consecutive patients starting their NOAC therapy at the cardiology outpatient clinic of the Medical Center Leeuwarden were included.

All patients with indications for NOAC for AF were included in the study. Atrial fibrillation patients who previously were treated with VKA were also included.

Exclusion criteria:

- Patients with persistent AF who required temporary NOAC therapy for scheduled cardioversion or pulmonary vein isolation.
- Patients using NOAC for off label indication (like stroke prevention in prosthetic or mechanical heart valves) were excluded.
- Atrial fibrillation patients who during the study switched to another NOAC

The clinic features a well-structured and nurse-based NOAC unit that operates in cooperation with hospital thrombosis service, and operates in accordance with Dutch guidelines governing integrated anticoagulation services[4]. These guidelines describe how NOACs should be prescribed and administered. According to these guidelines, the prescribing cardiologist and thrombosis service nurse are responsible for informing patients of the risks and benefits of NOAC therapy, initiating NOAC therapy, therapy follow-up consultations, patient monitoring, and information transfers to other healthcare providers included in the guidelines.

At our NOAC clinic, thrombosis service nurses initiate NOAC treatment in patients with AF who were previously diagnosed by a referring cardiologist. Using a checklist, thrombosis service nurses review the treatment indications, prescribed dose, presence of comorbidities, patient's renal function, and risk of thrombosis or bleeding as per CHA_2DS_2-VASc and HAS-BLED scores. They also provide the patients with relevant information about NOAC medications. Patients are routinely scheduled for 3, 6, and 12 month follow-up appointments. At these appointments, the nurse will carefully monitor and document patients' renal function and experiences such as side effects and minor bleeds with NOAC therapy. After the initial 12 months of NOAC therapy, patients are scheduled for once-yearly follow-ups.

The patients are also encouraged to contact the clinic if they experience adverse effects (including bleeding) or participate in planned interventions that might necessitate temporary NOAC discontinuation. Standardized question lists are used for adverse events at each clinic visit. These observations are subsequently documented in the patient's electronic medical record. The dose and type of NOAC may be changed during follow-up visits due to deteriorations in renal function, age, bleeding risk, medication side effects, or the patient's wishes after conferring with the referring cardiologist. Because of the clinic's well-structured follow-up processes, high quality and detailed data on patients treated with NOACs is readily available.

Study design

This was an observational population based cohort study of patients with AF who were referred to a regional NOAC outpatient clinic between February 2013 to October 2017.

All clinical data generated during the course of usual care were prospectively collected using the patients' electronic medical records. This EMR system (EPD vision) collects and stores patient NOAC treatment data and records contacts with other health providers for NOAC-related problems, side effects, bleeding episodes, cardiovascular events, cerebrovascular events, medication changes or discontinuations, and deaths. Patients were followed up for a maximum of 3 years.

Definitions of variables

The primary outcome measure was time to first minor bleeding event.. Secondary objectives were the risks factors (age, sex, renal function, CHA_2DS_2-VASc and HAS-BLED scores, blood pressure, and prior VKA therapy) for, type and rates of minor bleeding. Minor bleed was defined as every overt bleeding that does not fulfil the criteria of major or non-major clinically relevant bleeding according to International Society on Thrombosis and Haemostasis (S. Kaatz et al)[5].

Ethics

The Regional ethical committee reviewed the study protocol prior to the start of the study and decided that, in accordance with Dutch laws, for this retrospective study a full review was not required .

Statistics

Variables are presented as mean +/- standard deviation if normally distributed, or median and range if non-normally distributed. Categorical variables are presented using frequency counts and percentages.

Between-group differences in baseline characteristics were tested using the Chi Square test for categorical variables and F-test (ANOVA) or Kruskal Wallis test for continuous variables, depending on the data distribution. The time to first bleeding was depicted graphically using the Kaplan-Meier approach. Associations between minor bleeding and type of NOAC, as well as potential confounders (CHADS-VASc, HAS-BLED, previous VKA use , age, sex, renal function, medical history of bleeding) were assessed. After univariate analysis of all potential risk factors, those with a P-value <0.20 were

included in the initial multivariable model. A backward elimination strategy was used to achieve the most suitable model to estimate the adjusted relative risks with the final multivariable model only including the risk factors associated with minor bleeding.

To address the potential risk of informative censoring due to major bleeding or death, we performed three sensitivity analyses. [10] In this, the censored subjects were reclassified using three "worst case" scenario's: Scenario 1) The censored subjects with a major bleed were considered as experiencing a bleeding event – still censoring at time of death. Scenario 2) The censored subjects with either a major bleed or death were considered as experiencing a bleeding event. Scenario 3) The patients with either a major bleed or death were considered as NOT having a minor bleed over maximum follow-up time of 36 months.

By evaluating differences in risk estimates in the 3 scenario's, the impact of informative censoring will be assessed.

In cases where indication for NOAC was not longer present patients were censored (e.g. cancer, Watchman procedure).

A 2-tailed P-value <0.05 was considered to indicate statistical significance. All analyses were performed using SAS software, version 9.4 (SAS institute, Inc, Cary, NC).

RESULTS

Study population

The study population consisted of 875 consecutive patients with AF who visited the NOAC outpatient unit for initiation of treatment with apixaban (N=303), dabigatran (N=267) or rivaroxaban (N=305) for long-term ischemic stroke prophylaxis (Table 1). None of the participants used edoxaban. Median follow-up time was 15.7 months for the whole cohort (95% CI 14.9-16.6), 14.5 months (95% CI 13.8-15.9) for apixaban, 15.0 months (95% CI 14.0-17.0) for dabigatran, and 18.2 months (95% CI 16.2-23.7) for rivaroxaban. The median age was 70 years (range 39-98) and females accounted for 36% of the total study population. Most of the patients had received prior VKA therapy (52%) (N=455). Out of the 875 patients, 74 stopped due to an unplanned event that resulted in a lack of indication for NOAC treatment. Of these, 23 were administered apixaban, 31 were administered dabigatran, and 20 were administered rivaroxaban.

Freedom from minor bleeds

Figure 1 presents the Kaplan-Meier estimate for freedom from minor bleeds, stratified by NOAC. Overall rate of minor bleeds was 19.2 (95% CI 16.6-22.2) per 100 patient years of follow up. Bleeding rates for apixaban, dabigatran and rivaroxaban were 26 (95% CI 20.5-32.6) , 8.3 (95% CI 5.4-12.2) and 23 (95% CI 18.5-28.5) per 100 patient-years of follow-up. Our data show that apixaban and rivaroxaban were associated with more instances of minor bleeds, compared to dabigatran. Dabigatran had the fewest instances of minor bleeds over the whole follow-up period. The highest rate of minor bleeds for apixaban and rivaroxaban occurred during the first 3-12 months following NOAC initiation.

Using multivariable Cox regression analysis, type of NOAC was independently associated with minor bleeding. In this, apixaban and rivaroxaban had an 2.7-fold and 2.8-fold increased risk for minor bleeding (adjusted HR=2.72 (95% CI 1.74 to 4.27; p < 0.001) and 2.79 (95% CI 1.79 to 4.32; p < 0.001), respectively) , as compared to dabigatran.

As shown in Figure 2, we identified two other independent risk factors for minor bleeding , i.e. HAS-BLED ≥3 (adjusted HR=1.46 (95% CI 0.98 to 2.17; p = 0.061) and medical history of bleeding before NOAC therapy (adjusted HR=1.37 (95% CI 1.02 to 1.83; p = 0.034).

As shown in the supplementary table, no meaningful changes in risk estimates had occurred in either one of the sensitivity analyses. Only the HAS-BLED risk score showed a small increase in scenario 1 and 2. The risk estimates for type of NOAC were not affected, neither in univariate nor in the multivariable Cox regression analysis.

Reported types of minor bleeds from NOAC`s

Reported types of minor bleeds for each NOAC medication are listed in Table 2. There were significant differences in reported minor bleeds for the various NOAC medications. Our data showed that patients who received apixaban (25% (n=76 out of 303, *p*-value <0.001)) and rivaroxaban (28% (n=85 out of 305, *p*-value<0.001)) reported the most minor bleeds. Apixaban and rivaroxaban users experienced significantly more minor bleeds such as hematoma (defined as only bruises, no skin echymosis), nose and eye bleed. Cumulative minor bleed was higher in these two groups as well.

Number of deaths

As shown in Table 3, 22 patients (2.5%) had died during the 36 months follow-up. Of these patients, 16 (1.8%) had not experienced a minor or major bleed prior to the time of death.

DISCUSSION

Our data detail the treatment durations and minor bleeds associated with three different NOAC medications (apixaban, dabigatran and rivaroxaban) following initiation and long-term follow-up within our NOAC clinical unit. This is one of the few long-term population-based follow-up studies to compare multiple NOAC medications administered through a NOAC specialty clinic. At this moment there is lack of data on this subject worldwide with which we can compare our results.

Our clinical practice data showed significant difference in rate and type of minor bleeds between three NOAC medications. Potential risk factors for minor bleeds were type of NOAC, high HAS-BLED score and previous VKA use.

Dabigatran had the lowest risk of minor bleeds where apixaban and rivaroxaban showed no significant difference. HAS-BLED score higher than 3 was associated with higher incidence of minor bleeds. This could be explained by a simple fact that higher HAS-BLED score corresponds with higher chance of bleeding. History of previous VKA use also led to higher risk of minor bleeds. There is no exact explanation for this fact but we can speculate that patients who previously used VKA are more critical or experienced when it comes to side effects or bleedings caused by anticoagulation therapy in general. Another reason for previous VKA users having more minor bleeds could be that they switched to a NOAC because of bleeding on VKA, in the hope of less bleeding on NOAC.

The highest rates of minor bleeds were measured within 3-12 months after initiation of therapy. Cumulative minor bleeds were most present in apixaban and rivaroxaban population. Hematoma (bruises), nose and retinal bleed were more present in apixaban and rivaroxaban population. This could be due to a same medication group (anti-Xa) effect. These type of minor bleeds together with gastro-intestinal minor bleeds are the most common among our population.
Minor bleeding rates of rivaroxaban in Dresden study (35.8 per 100 patient years) are comparable with what we found in our population using rivaroxaban (23 per 100 patient years).

This study had several limitations. Our data were collected retrospectively and our cohort was non-randomized. Minor bleeds were reported using standard adverse events questionnaires, administered by specialty nurses. There is a chance that patients don`t report all of the minor bleeds because some of them could be embarrassing or patient could feel uncomfortable to report it (such us vaginal or rectal bleeding). This can result in underreporting of minor bleeds. Furthermore, in evaluating minor bleeding, the occurrence of competing events could bias the risk estimates for minor bleeding. We performed three sensitivity analyses addressing this issue and found no evidence

for informative censoring. The risk estimated for type of NOAC were not affected, neither in univariate nor in the multivariable Cox regression analysis. In this, we feel that informative censoring, when even present, was very limited.

HAS-BLED score was designed to predict major bleeding. Exploration of each component of HAS-BLED score as it might be related specifically to minor bleeding should be part of any further research.

One strength of this study was our relatively long duration period of 36 months compared to other studies. We also examined a large group of patients and obtained detailed follow-up records. We have prospectively collected data on patients who used VKA therapy prior to NOAC therapy and determined their reasons for switching. Further research should focus on management and costs of management of minor bleeds and on impact of minor bleeds on patient adherence.

CONCLUSION

Our data showed that minor bleeds are common in novel NOAC users, especially when using apixaban and rivaroxaban. In the latter two NOACs, hematoma (bruises) and nose bleeds were more frequently observed and accounted for the difference with dabigatran. Besides type of NOAC, a higher HAS-BLED score and novel anticoagulant drug use were associated with an increased risk of minor bleeding.

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TABLES AND FIGURES

Table 1. Baseline characteristics

Variable	Apixaban N=303	Dabigatran N=267	Rivaroxaban N=305	Total N=875	p-value
Age	72 ± 9	69 ± 9	69 ± 9	70 ± 9	<0.001
Male	184 (61%)	174 (65%)	201 (66%)	559 (64%)	0.36
eGFR ml/min at start	75 (63-87)	76 (65-86)	72 (63-82)	74 (63-85)	0.022
Systolic blood pressure	142 ± 19	143 ± 20	140 ± 18	142 ± 19	0.17
Diastolic blood pressure	84 ± 12	85 ± 12	83 ± 10	84 ± 11	0.16
HAS-BLED score					
0	38 (13%)	46 (17%)	42 (14%)	126 (14%)	0.14
1	124 (41 %)	118 (44%)	130 (43%)	372 (43%)	
2	94 (31%)	83 (31%)	103 (34%)	280 (32%)	
3	34 (11%)	17 (6%)	23 (8%)	74 (9%)	
4 or >	11 (4 %)	3 (1%)	5 (2%)	19 (2%)	
Unknown	2	0	2	4	
CHA2DS2-VASc score					
0-1	55 (18%)	65 (24%)	58 (19%)	178 (20%)	0.026
2	75 (25%)	84 (32%)	97 (32%)	256 (29%)	
3	67 (22%)	56 (21%)	78 (26%)	201 (23%)	
4	59 (20%)	34 (13%)	42 (14%)	135 (16%)	
>5	46 (15%)	28 (10%)	29 (9%)	103 (12%)	
Unknown	1	0	1	2	
Prior VKA therapy					
Yes	150 (49%)	144 (54%)	161 (53%)	455 (52%)	0.54
Reduced dose of NOAC*	57 (19%)	68 (26%)	42 (14%)	167 (19%)	0.002

Categorical variables are presented as N (%), continuous variables are presented as mean ± SD or median (Q1-Q3), and analyzed with ANOVA or Kruskal-Wallis tests, as appropriate. The p-values (test for independence between NOAC medications and the respective baseline variable) tested the null hypothesis of no differences among the three types of NOAC medications.

* Reduced dose of NOAC means dabigatran 110 mg, apixaban 2,5 mg an rivaroxaban 15 mg.

Table 2. Reported minor and major bleeding

Bleeding	**Apixaban N=303**	**Dabigatran N=267**	**Rivaroxaban N=305**	**Total N=875**	***p*-value**
Minor Bleeding Total	76 (25 %)	26 (10 %)	86 (28%)	188 (21%)	<0.001
Cumulative Minor Bleeding 0 1 2 3 Unknown	 227 (75%) 67 (22%) 7 (2%) 1 (0,5%) 1	 241 (90%) 26 (10%) 0 (0%) 0 (0%)	 219 (72%) 71 (23%) 10 (3%) 3 (1%) 2	 687 (79%) 164 (19%) 17 (2%) 4 (0,5%) 3	<0.001
Hematoma (bruises)	37 (12%)	9 (3%)	36 (12%)	82 (9%)	<0.001
Nose	19 (6%)	5 (2%)	35 (11%)	59 (7%)	<0.001
Retinal	12 (4%)	2 (1%)	12 (4%)	26 (3%)	0.036
Gastro-Intestinal	9 (3%)	6 (2%)	10 (3%)	25 (3%)	0.79
Teeth Gum	3 (1%)	0 (0%)	2 (1%)	5 (0,6%)	0.33
Vaginal	1 (0,3%)	2 (0,8%)	3 (1%)	6 (0,7%)	0.69
Haemoptysis	1 (0,3%)	1 (0,4%)	0 (0%)	2 (0,2%)	0.55
After Surgery	0 (0%)	0 (0%)	1 (0,3%)	1 (0,1%)	1.00
Other	2 (0,7%)	1 (0,4%)	1 (0,3%)	4 (0,5%)	0.85
Major (cranial)	1 (0,3%)	2 (0,8%)	2 (0,7%)	5 (0,6%)	0.87

Table 3. Occurrence of death

Bleeding	**Apixaban N=303**	**Dabigatran N=267**	**Rivaroxaban N=305**	**Total N=875**
Death	10 (3.3 %)	4 (1.5 %)	8 (2.6%)	22 (2.5%)
Major bleeding or death[#]				
major bleeding	1 (0.3%)	2 (0.8%)	2 (0.7%)	5 (0.6%)
death	8 (2.6%)	3 (1.1%)	5 (1.7%)	16 (1.8%)

No double counting within patients, first occurrence counted. (In apixaban there were 2 deaths after a minor bleed, in dabigatran there was 1 death after a major bleed, and in rivaroxaban there was 1 death after a major bleed and 2 deaths after a minor bleed.)

Figure 1. Kaplan-Meier curve for freedom from minor bleeds for apixaban, dabigatran, and rivaroxaban

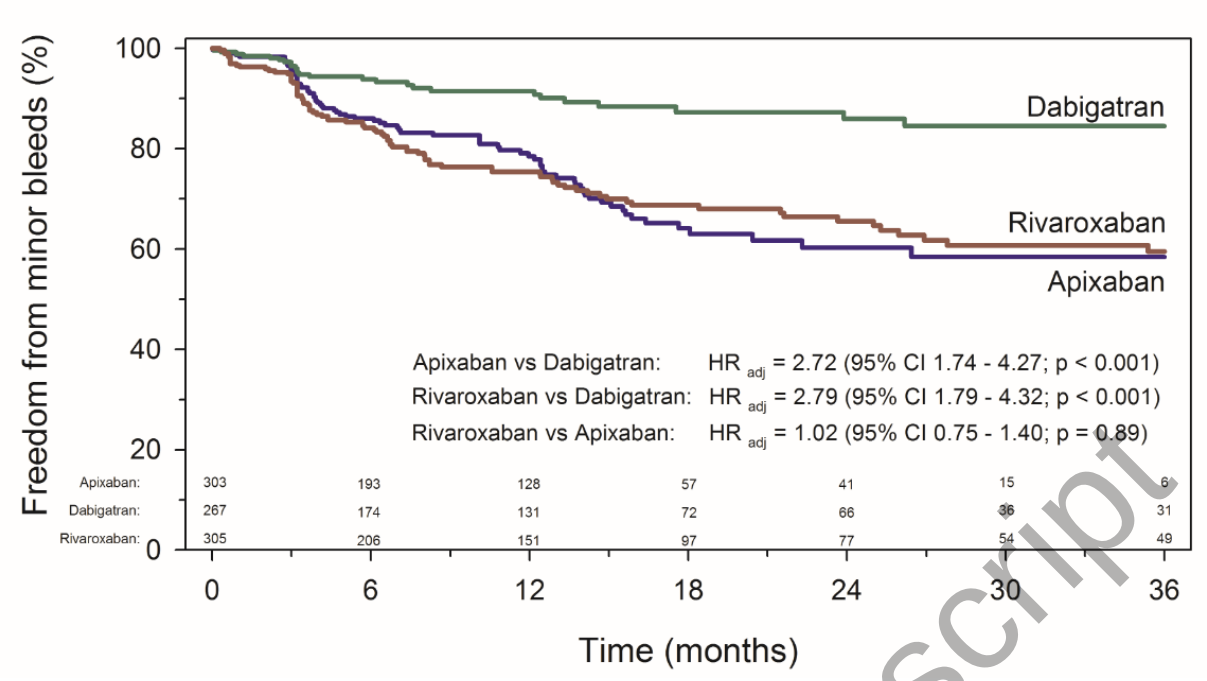

Figure 2. Univariate and multivariable analysis of minor bleeding